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Keio University School of Medicine

The First Clinical Study Shows a Key NAD⁺ Intermediate NMN Safe for Human Use

A research team at Keio University has shown for the first time that nicotinamide mononucleotide (NMN), a promising compound for anti-aging intervention, can be safely administered to healthy humans. The Keio University research team was led by Prof. Hiroshi Itoh of the Department of Internal Medicine (Endocrinology, Metabolism, and Nephrology,), Prof. Kazuo Tsubota of the Department of Ophthalmology, Prof. Masato Yasui of the Department of Pharmacology, and Prof. Hideyuki Okano of the Department of Physiology, and the study was conducted in collaboration with Prof. Shin-ichiro Imai of Washington University School of Medicine in St. Louis.

Recent studies in animal models have shown that the administration of NMN increases the amount of nicotinamide adenine dinucleotide (NAD⁺) in various organs and improves age-associated functional decline and disease conditions. However, the safety of NMN in humans have remained unclear.

Since 2016, the research team has conducted a clinical trial study to investigate the safety of single administration of NMN in ten healthy men and has confirmed that (1) it can be safely administered and that (2) it is effectively metabolized in the body. This study is expected to inform future treatment of age-associated diseases.

The results of this research were published in *Endocrine Journal* on November 2, 2019.

1. Research Background

On November 20, 2015, the Keio University School of Medicine and Washington University School of Medicine in St. Louis, a leader in aging research, entered into a five-year academic cooperation agreement to promote joint research in the areas of aging, longevity, and metabolic disease.

Our research team is currently conducting several projects to prevent age-associated diseases, with a keen awareness of the acceleration of aging in our society. One such project aims to study a preventive and therapeutic potential of a key NAD⁺ intermediate, nicotinamide mononucleotide (NMN), whose safety in humans is the subject of this clinical study.

Recent research led by the Imai Lab at Washington University School of Medicine in St. Louis has revealed that the decrease of NAD⁺, which is naturally occurring throughout the body, is linked to age-associated functional decline and the onset of diabetes and other age-associated diseases.

That revelation prompted a clinical study that investigated the safety of administering NMN, a key intermediate to generate NAD⁺ in the body, to human patients. The study was led by the principal investigator Prof. Hiroshi Itoh and co-investigators including Prof. Kazuo Tsubota, Prof. Masato Yasui, Prof. Hideyuki Okano. Prof. Shin-ichiro Imai of Washington University School of Medicine in St. Louis provided technical consultation in research planning and execution. (See [5. Related Press Release](#) below)

2. Research Significance and Future Development

In this study, ten healthy men between the ages of 40 and 60 were given a single oral dose of 100, 250, or 500 mg of NMN. The single oral administrations of NMN did not cause any significant changes in heart rate or blood pressure, and blood and urine tests, which analyze liver and kidney function, did not exceed normal levels. They also did not change eye functions or affect the quality of sleep. Also, when measuring the number of plasma metabolites produced from NMN, the team found that their amounts increased in accordance with dosage.

These results suggest that orally administered NMN is effectively metabolized in the human body and can be safely used at single doses up to 500 mg.

Although past studies looked at treatments that would increase tissue NAD⁺ to prevent age-associated diseases, NMN is now one of the leading candidates for activating the sirtuin¹ enzymes that play important roles in mammalian aging/longevity control.

This clinical study shows, for the first time, that NMN can be safely administered to humans, and we can expect further development of research into the application of NMN for the prevention and treatment of age-associated diseases.

With these results, the research team is planning a long-term administration study of NMN in healthy subjects in order to critically assess the safety of long-term administration of NMN and clarify the pharmacokinetics of NAD⁺ and other molecules (Japan Registry of Clinical Trials ID: jRCTs031180242).

Going forward, the further development of clinical research will promote a nutritional approach based on scientific evidence using NMN for the treatment and prevention of aging-associated diseases.

This study, however, was not focused on developing NMN as a drug, but was conducted as a clinical study aiming at obtaining evidence for the safety of NMN, and Keio University and Keio University Hospital did not recruit trial participants.

3. Notes

This study was conducted with the support and cooperation of the Longevity Initiative (led by director Hideyuki Okano) within the Program for the Advancement of Research in Core Projects, part of the Keio University Global Research Institute (led by director Masato Yasui).

NMN used in this study was provided by Oriental Yeast Co., Ltd.

4. Research Paper

Title: Effect of oral administration of nicotinamide mononucleotide on clinical parameters and nicotinamide metabolite levels in healthy Japanese men

Japanese Title: 健常日本人男性におけるニコチンアミド・モノヌクレオチド経口投与の臨床指標とニコチンアミド代謝産物に対する影響

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5. Related Press Release (English)

The World's First Human Clinical Study of the Age-Regulating Compound Nicotinamide Mononucleotide

<https://www.keio.ac.jp/en/press-releases/2016/Dec/27/49-19313/>

[Glossary]

¹ Sirtuin

Sirtuins are enzymes that modify various proteins in an NAD⁺-dependent manner. They play important roles in controlling aging and longevity in a variety of organisms.

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*A color version of this press release is available. Please contact the above address for more information.